REMARKS

Claims 1-6, 8, 10 and 15-23 and 25-35 are pending in the application. Claim 1 and 16 are currently amended. Claims 2-6, 8, 10, 15-23 and 25-35 were previously presented, and claims 7, 9, 11-14 and 24 were previously canceled.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the January 11, 2005 Office Action.

Rejection under 35 USC § 112, First Paragraph

The Examiner maintained the rejection of claims 1-6, 8, 10 and 15-35 under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification as set forth in the previous Office Action. In particular, the Examiner indicated that the references submitted to demonstrate enablement for the additional compounds recited in claim 1 were dated after the effective filing date of the subject application, and thus do not provide enabling support.

In response, applicants are submitting herewith supplementary abstracts of references which were available prior to the filing date of the subject application, and therefore provide enabling support for the following additional compounds recited in claim 1 as amended: amyloid aggregation inhibitors, secretase inhibitors, neuronal antiinflammatory agents and estrogen-like agents. The references supporting each specific additional recited compound are listed hereinbelow for the convenience of the Examiner:

Muscarinic Agonists

1. Hollander E. Davidson M. Mohs RC. Horvath TB. Davis BM. Zemishlany Z. Davis KL. RS 86 in the treatment of Alzheimer's disease: cognitive and biological effects.
Biological Psychiatry. 22(9):1067-78, 1987 Sep.

2. Fisher A. Heldman E. Gurwitz D. Haring R. Karton Y. Meshulam H. Pittel Z. Marciano D. Brandeis R. Sadot E. Barg Y. Pinkas-Kramarski R. Vogel Z. Ginzburg I. Treves TA. Verchovsky R. Klimowsky S. Korczyn AD. M1 agonists for the treatment of Alzheimer's disease. Novel properties and clinical update. Annals of the New York Academy of Sciences. 777:189-96, 1996 Jan 17.

3. Nakahara N. Iga Y. Saito Y. Mizobe F. Kawanishi G. Beneficial effects of FKS-508 (AF102B), a selective M1 agonist, on the impaired working memory in AF64A-treated rats. Japanese Journal of Pharmacology. 51(4):539-47, 1989 Dec.

4. Bromidge SM. Brown F. Cassidy F. Clark MS. Dabbs S. Hadley MS. Hawkins J. Loudon JM. Naylor CB. Orlek BS. Riley GJ. Design of [R-(Z)]-(+)-alpha-(methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitri le (SB 202026), a functionally selective azabicyclic muscarinic M1 agonist incorporating the N-methoxy imidoyl nitrile group as a novel ester bioisostere. Journal of Medicinal Chemistry. 40(26):4265-80, 1997 Dec 19.

5. Bodick NC. Offen WW. Shannon HE. Satterwhite J. Lucas R. van Lier R. Paul SM. The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. Alzheimer Disease & Associated Disorders. 11 Suppl 4:S16-22, 1997.

6. Plate R. Plaum MJ. de Boer T. Andrews JS. Rae DR. Gibson S. Synthesis and muscarinic activities of 3-(pyrazolyl)-1,2,5,6-tetrahydropyridine derivatives. Bioorganic & Medicinal Chemistry. 4(2):227-37, 1996 Feb.

7. Fisher A. Heldman E. Gurwitz D. Haring R. Karton Y. Meshulam H. Pittel Z. Marciano D. Brandeis R. Sadot E. Barg Y. Pinkas-Kramarski R. Vogel Z. Ginzburg I. Treves TA. Verchovsky R. Klimowsky S. Korczyn AD. M1 agonists for the treatment of Alzheimer's disease. Novel properties and clinical update. Annals of the New York Academy of Sciences. 777:189-96, 1996 Jan 17.

Amyloid Aggregation Inhibitors

1. Emmerling MR. Spiegel K. Watson MD. Inhibiting the formation of classical C3-convertase on the Alzheimer's beta-amyloid peptide. *Immunopharmacology. 38(1-2):101-9, 1997 Dec.*

2. Carr DB. Goate A. Phil D. Morris JC. Current concepts in the pathogenesis of Alzheimer's disease. *American Journal of Medicine. 103(3A):3S-10S, 1997 Sep 22.*

3. Parnetti L. Senin U. Mecocci P. Cognitive enhancement therapy for Alzheimer's disease. The way forward. *Drugs. 53(5):752-68, 1997 May.*

Secretase Inhibitors

Maruyama K. Kametani F. Usami M. Yamao-Harigaya W. Tanaka K. "Secretase," Alzheimer amyloid protein precursor secreting enzyme is not sequence-specific. Biochemical & Biophysical Research Communications. 179(3):1670-6, 1991 Sep 30.

Neuronal Anti-Inflammatory Agents

1. Verbeek MM. Otte-Holler I. Ruiter DJ. de Waal RM. [Inflammatory mechanisms in the pathogenesis of Alzheimer's disease]. Tijdschrift voor Gerontologie en Geriatrie. 28(5):213-8, 1997 Oct.

2. Scheltens P. van Gool WA. Emerging treatments in dementia. European Neurology. 38(3):184-9, 1997.

3. Cummings JL. Mendez MF. Alzheimer's disease: cognitive and behavioral pharmacotherapy. Connecticut Medicine. 61(9):543-52, 1997 Sep.

4. Senin U. Cherubini A. Palumbo B. Mecocci P. Pharmaceutical treatment of cognitive disorders in Alzheimer's disease. Functional Neurology. 12(3-4):211-2, 1997 May-Aug.

5. Parnetti L. Senin U. Mecocci P. Cognitive enhancement therapy for Alzheimer's disease. The way forward. Drugs. 53(5):752-68, 1997 May.

6. Aisen PS. Inflammation and Alzheimer's disease: mechanisms and therapeutic strategies. Gerontology. 43(1-2):143-9, 1997.

Estrogen-like Agents

1. Lerner A. Koss E. Debanne S. Rowland D. Smyth K. Friedland R. Smoking and oestrogen-replacement therapy as protective factors for Alzheimer's disease. Lancet. 349(9049):403-4, 1997 Feb 8.

2. Mook-Jung I. Joo I. Sohn S. Kwon HJ. Huh K. Jung MW. Estrogen blocks neurotoxic effects of beta-amyloid (1-42) and induces neurite extension on B103 cells. Neuroscience Letters. 235(3):101-4, 1997 Oct 17.

3. Jorm AF. Alzheimer's disease: risk and protection. Medical Journal of Australia. 167(8):443-6, 1997 Oct 20.

4. Beckmann CR. Alzheimer's disease: an estrogen link? Current Opinion in Obstetrics & Gynecology. 9(5):295-9, 1997 Oct.

5. Schneider LS. Farlow MR. Pogoda JM. Potential role for estrogen replacement in the treatment of Alzheimer's dementia. American Journal of Medicine. 103(3A):46S-50S, 1997 Sep 22.

6. Birge SJ. Mortel KF. Estrogen and the treatment of Alzheimer's disease. American Journal of Medicine. 103(3A):36S-45S, 1997 Sep 22.

7. Schneider LS. Farlow M. Combined tacrine and estrogen replacement therapy in patients with Alzheimer's disease. Annals of the New York Academy of Sciences. 826:317-22, 1997 Sep 26.

8. Kawas C. Resnick S. Morrison A. Brookmeyer R. Corrada M. Zonderman A. Bacal C. Lingle DD. Metter E. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging.[erratum appears in Neurology 1998 Aug;51(2):654]. Neurology. 48(6):1517-21, 1997 Jun.

9. Henderson VW. The epidemiology of estrogen replacement therapy and Alzheimer's disease. Neurology. 48(5 Suppl 7):S27-35, 1997 May.

Without conceding the correctness of the Examiner's grounds for rejection, but in order to expedite the prosecution of the subject application, applicants have herein amended claim 1 to delete the additional compounds encompassed by "tau kinase inhibitors" and "neurotrophic factors." Applicants reserve the right to pursue the deleted subject matter in a continuing application.

Applicants submit that, in view of the cited references, the individual of ordinary skill in the art would readily be able to identify specific members of any of the aforementioned classes and formulate them with the active ingredient of instant formula I using principles and procedures that are common knowledge in the art, the guidance provided by the instant specification and readily available publications. For the foregoing reasons, applicants respectfully submit that the specification is enabling to those skilled in the art seeking to formulate the compounds of formula I into the pharmaceutical compositions that include the classes of active ingredients recited in claim 1, as amended.

Accordingly, applicants respectfully submit that claims 1-6, 8, 10 and 15-23 and 25-35 are patentable under 35 USC § 112, first paragraph, and therefore request that the Examiner to withdraw the rejection.

Rejection Under The Judicially Created Doctrine Of Obviousness-Type Double Patenting

Claims 1-6, 8, 10, 15-19, 22, 24-27 and 30-35 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of copending Application No. 10/348,381. As the aforesaid rejection is provisional, pending the disposition of the status of the allegedly conflicting claims of copending Application No. 10/348,381, applicants therefore continue to request that the instant provisional rejection be held in abeyance until the status of the claims of Application No. 10/348,381 is clarified. In addition, applicants continue to request that the instant rejection be held in abeyance until the instant claims are found to be otherwise allowable.

Claims 1-6, 8, 10, 15-19, 22, 24-28 and 30-35 also remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/348,399. As this rejection is also provisional, pending the disposition of the status of the allegedly conflicting claims of copending Application No. 10/348,399, applicants therefore request that the instant provisional rejection remain held in abeyance until the status of the claims of Application No. 10/348,399 is clarified. In addition, applicants continue to request that the instant rejection be held in abeyance until the instant claims are found to be otherwise allowable.

Rejection under 35 USC § 112, Second Paragraph

The Examiner maintained the ground labeled "c)" for rejection of claims 1, 8, 10 and 15-35 under 35 USC § 112, second paragraph, set forth in the previous Office Action.

In response to the rejection set forth in paragraph c) of the previous Office Action, applicants have herein amended claim 16 to correct the nomenclature for the "acetamide" species therein wherein the point of attachment of the ring system to the acetamide N atom was inadvertently and unintentionally denoted as position "1." Accordingly, the argument made in applicants' prior paper regarding antecedent basis for this species is revised to assert that claim 1 recites that formula 1 may have R^1 = H, R^2 = H and R^3= -$CONR^5R^6$ wherein R^5 may be H and R^6 may be C_1 alkyl which corresponds to the compound N-[10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl]acetamide. Applicants submit that sufficient antecedent basis exists for this species in the subject specification.

Applicants therefore believe that currently amended claim 1 and claims 8, 10, 15-23 and 25-35 are patentable under 35 USC § 112, second paragraph, and respectfully request the Examiner to withdraw the remaining rejection.

In view of the amendments set forth herein and remarks above, the applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the

subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: April 11, 2005

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department
150 East 42nd Street – 5th Floor
New York, NY 10017-5755
(212) 733-3381

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Ovid MEDLINE(R) <1966 to March Week 5 2005>

#	Search History	Results
1	(muscarinic and alzheimer).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	516
2	limit 1 to yr=1902 - 1998	361
3	limit 2 to yr=1902 - 1997	324
4	from 3 keep 3, 7, 11, 15, 24, 69...	7

Results of your search: **from 3 [limit 2 to yr=1902 - 1997] keep 3, 7, 11, 15, 24, 69...**
Results available: **7**
Results displayed: **1-7** Logoff

Citation 1.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
3651528
Authors
Hollander E. Davidson M. Mohs RC. Horvath TB. Davis BM. Zemishlany Z. Davis KL.
Institution
Psychiatry Service, Bronx VA Medical Center, NY 10468.
Title
RS 86 in the treatment of **Alzheimer**'s disease: cognitive and biological effects.
Source
Biological Psychiatry. 22(9):1067-78, 1987 Sep.
Abstract
Twelve patients who met Research Diagnostic Criteria for **Alzheimer**'s disease (AD) completed a double-blind crossover study comparing oral RS 86, a long-acting and specific **muscarinic** agonist, with placebo. Cognitive and noncognitive effects were assessed with the **Alzheimer**'s Disease Assessment Scale (ADAS). RS 86 was found to improve ADAS test scores consistently (both cognitive and noncognitive subscales) in seven patients, with a clinically obvious improvement in only two patients. RS 86 produced a significant increase in peak nocturnal cortisol levels, and this increase correlated with improvement on ADAS testing. Similarly, there was a 38% increase in amplitude of the P300 evoked potential with RS 86. The biological findings suggest that RS 86 was effective only to the extent that it enhanced central cholinergic activity.

Citation 2.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
8624083
Authors
Fisher A. Heldman E. Gurwitz D. Haring R. Karton Y. Meshulam H. Pittel Z. Marciano D.

Brandeis R. Sadot E. Barg Y. Pinkas-Kramarski R. Vogel Z. Ginzburg I. Treves TA. Verchovsky R. Klimowsky S. Korczyn AD.

Institution

Israel Institute for Biological Research, Ness-Ziona, Israel.

Title

M1 agonists for the treatment of **Alzheimer**'s disease. Novel properties and clinical update. [Review] [21 refs]

Source

Annals of the New York Academy of Sciences. 777:189-96, 1996 Jan 17.

Abstract

The AF series compounds, AF102B and congeners of AF150(S), are functionally selective agonists for m1 **muscarinic** receptors (m1AChRs). This is shown in stable transfected CHO and PC12 cells (PC12M1) with m1m5AChRs and m1AChRs, respectively. AF102B and AF150(S) are partial agonists, but AF150, AF151, and AF151 (S) are full agonists in stimulating phosphoinositides hydrolysis or arachidonic acid release in these cells. Yet, all these compounds behave as antagonists when compared with carbachol in elevating cAMP levels. In PC12M1 cells, unlike carbachol, the AF series compounds induce only minimal to moderate neurite outgrowth. Yet, these agonists synergize strongly with NGF, which by itself mediates only a mild response. Stimulation of m1AChRs by AF102B, AF150(S) and AF151(S) in PC12M1 cells enhances secretion of beta/A4 amyloid precursor protein derivatives (APPs). The enhanced APPs secretion induced by AF102B is potentiated by NGF. AF102B also stimulates APPs secretion from rat cortical slices. Stimulation of m1AChR in PC12M1 cells with carbachol or AF102B decreases tau phosphorylation as indicated by specific tau-1 mAb and alkaline phosphatase treatment. Due to the above mentioned properties m1 agonists may be of unique value in delaying the progression of **Alzheimer**'s disease (AD). The AF series compounds show a wide safety margin and improve memory and learning deficits in animal models for AD. There is a dearth of clinical reports on m1 agonists. These include studies on AF102B and xanomeline, another m1 selective agonist. We tested AF102B in escalating doses of 20, 40, 60 mg, tid, po, (each dose for 2 weeks) for a total of 10 weeks. This was a single-blind placebo-controlled, parallel-group study in patients with probable AD. AF102B was significantly effective at 40 and 60 mg, tid in the ADAS, ADAS-cognitive and ADAS-word recognition scales. [References: 21]

Citation 3.

Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier

2615046

Authors

Nakahara N. Iga Y. Saito Y. Mizobe F. Kawanishi G.

Institution

Research Institute of Life Science, Snow Brand Milk Products Co., Ltd., Tochigi, Japan.

Title

Beneficial effects of FKS-508 (AF102B), a selective M1 agonist, on the impaired working memory in AF64A-treated rats.

Source

Japanese Journal of Pharmacology. 51(4):539-47, 1989 Dec.

Abstract

The effects of FKS-508 [AF102B; cis-2-methylspiro(1,3-oxathiolane-5,3')quinuclidine], a selective M1 **muscarinic** receptor agonist, were examined to predict the possible activity on memory disorders using a T-maze and radial-arm maze task in experimental amnesia models. The amnesia models were produced by bilateral intracerebroventricular injection of ethylcholine

aziridinium ion (AF64A), a selective cholinotoxin, in rats. Repeated administrations of FKS-508 (5 mg/kg/day, i.p.) for 5 weeks significantly ameliorated impaired performance of AF64A-treated rats (AF64A-rats) in a delayed alternation task in the T-maze. Repeated administrations of FKS-508 (1 and 5 mg/kg/day, p.o.) for 5 weeks significantly ameliorated acquisition failures of AF64A-rats in a radial-arm maze task. Single administration of FKS-508 (1 and 5 mg/kg, p.o.) significantly reduced the incorrect choices of AF64A-rats in a radial-arm maze task with 6 hr-delay time. No abnormalities in general behaviors, such as loss of appetite and ataxia, were observed in rats treated with FKS-508 repeatedly during 5 weeks. Our present results showed that FKS-508 can ameliorate memory impairments in AF64A-rats with central cholinergic hypofunction without causing any behavioral abnormalities. FKS-508 may be considered as a candidate for the clinical examination of the cholinergic hypothesis of senile dementia of the **Alzheimer** type.

Citation 4.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9435896

Authors
Bromidge SM. Brown F. Cassidy F. Clark MS. Dabbs S. Hadley MS. Hawkins J. Loudon JM. Naylor CB. Orlek BS. Riley GJ.

Institution
Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, Harlow, Essex, U.K.

Title
Design of [R-(Z)]-(+)-alpha-(methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitri le (SB 202026), a functionally selective azabicyclic **muscarinic** M1 agonist incorporating the N-methoxy imidoyl nitrile group as a novel ester bioisostere.

Source
Journal of Medicinal Chemistry. 40(26):4265-80, 1997 Dec 19.

Abstract
Loss of cholinergic function is believed to be implicated in the cognitive decline associated with senile dementia of the **Alzheimer** type (SDAT). The disease is characterized by progressive loss of **muscarinic** receptors located on nerve terminals while postsynaptic **muscarinic** M1 receptors appear to remain largely intact. **Muscarinic** agonists acting directly on postsynaptic receptors offer the prospect of countering the cholinergic deficit in SDAT. This study describes a novel series of azabicyclic **muscarinic** agonists, which incorporate an oxime ether or modified oxime ether group as an ester bioisostere. Modification of the oxime ether function by the introduction of electron withdrawing groups led to the finding that the (Z)-N-methoxy imidoyl nitrile group serves as a stable methyl ester bioisostere. This culminated in the discovery of the quinuclidinyl N-methoxy imidoyl nitrile R-(+)-(Z)-5g which is a functionally selective **muscarinic** M1 partial agonist currently in phase III clinical trials for the treatment of SDAT. The selective profile of R-(+)-(Z)-5g can be rationalized in terms of the relative affinity of the compound at **muscarinic** receptor subtypes, the degree of agonist efficacy, and brain penetrancy.

Citation 5.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9339268

Authors
Bodick NC. Offen WW. Shannon HE. Satterwhite J. Lucas R. van Lier R. Paul SM.
Institution
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.
Title
The selective **muscarinic** agonist xanomeline improves both the cognitive deficits and behavioral symptoms of **Alzheimer** disease.
Source
Alzheimer Disease & Associated Disorders. 11 Suppl 4:S16-22, 1997.
Abstract
The therapeutic effects of selective cholinergic replacement using oral xanomeline, an m1/m4 receptor agonist, were assessed in a multicenter study of 343 patients with **Alzheimer** disease (AD). Patients were randomized to parallel treatment arms (placebo, 25, 50, and 75 mg t.i.d. xanomeline) and followed through 6 months of double-blind therapy and 1 month of single-blind placebo washout. Completer analysis, using the cognitive subscale of the **Alzheimer**'s Disease Assessment Scale (ADAS-Cog), revealed a significant treatment effect (75 mg t.i.d. vs. placebo; p = 0.045). Similar assessment of global status, using the Clinician's Interview-Based Impression of Change, was also significant (75 mg t.i.d. vs. placebo; p = 0.022). Treatment Emergent Signs and Symptoms analysis of the **Alzheimer**'s Disease Symptomatology Scale, revealed highly significant (p < or = 0.002) dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. On end-point analysis, the Nurses' Observational Scale for Geriatric Patients also showed a significant dose-response relationship (p = 0.018). The improvement in ADAS-Cog provides the first clinical evidence of involvement of the m1 **muscarinic** receptor in cognition. Furthermore, the favorable effects of xanomeline on disturbing behaviors suggest a novel approach for treatment of the noncognitive symptoms of AD. Although adverse effects (mainly gastrointestinal) associated with the oral formulation appear to limit its use, a large-scale study investigating the safety and efficacy of transdermal xanomeline is under way.

Citation 6.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
8814880
Authors
Plate R. Plaum MJ. de Boer T. Andrews JS. Rae DR. Gibson S.
Institution
Department of Medicinal Chemistry, Scientific Development Group N.V. Organon, The Netherlands.
Title
Synthesis and **muscarinic** activities of 3-(pyrazolyl)-1,2,5,6-tetrahydropyridine derivatives.
Source
Bioorganic & Medicinal Chemistry. 4(2):227-37, 1996 Feb.
Abstract
A series of 3-(pyrazolyl)-1,2,5,6-tetrahydropyridine derivatives (B) was synthesized and tested for **muscarinic** activity in receptor binding assays using [3H]-oxotremorine-M (3H-OXO-M) and [3H]-pirenzepine (3H-PZ) as ligands. Potential **muscarinic** agonistic or antagonistic properties of the compounds were determined using binding studies measuring their potencies to inhibit the binding of 3H-OXO-M and 3H-PZ. Preferential inhibition of 3H-OXO-M binding was used as an indicator for potential **muscarinic** agonistic properties; this potential was confirmed in functional studies on isolated organs. All compounds with agonistic properties

showed 3H-PZ/3H-OXO-M potency ratios in excess of 20. In contrast, for antagonists this ratio was found to be close to unity. Mono-halogenation resulted in compounds (4b and 4d) with M3 agonistic properties as shown by their atropine sensitive stimulant properties in the guinea pig ileum, but with very little or no M1 activity. Some minor in vivo effects were observed for both these compounds, with the iodinated compound 4d inducing salivation. Compound 4d also showed some positive mnemonic properties in rats where spatial short-term memory had been compromised by temporary cholinergic depletion. These data indicate that some M3 agonism may be desired in therapeutic agents aimed at the treatment of the cognitive deficits of **Alzheimer**'s disease patients.

Citation 7.

Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier

8624083

Authors

Fisher A. Heldman E. Gurwitz D. Haring R. Karton Y. Meshulam H. Pittel Z. Marciano D. Brandeis R. Sadot E. Barg Y. Pinkas-Kramarski R. Vogel Z. Ginzburg I. Treves TA. Verchovsky R. Klimowsky S. Korczyn AD.

Institution

Israel Institute for Biological Research, Ness-Ziona, Israel.

Title

M1 agonists for the treatment of **Alzheimer**'s disease. Novel properties and clinical update. [Review] [21 refs]

Source

Annals of the New York Academy of Sciences. 777:189-96, 1996 Jan 17.

Abstract

The AF series compounds, AF102B and congeners of AF150(S), are functionally selective agonists for m1 **muscarinic** receptors (m1AChRs). This is shown in stable transfected CHO and PC12 cells (PC12M1) with m1m5AChRs and m1AChRs, respectively. AF102B and AF150(S) are partial agonists, but AF150, AF151, and AF151 (S) are full agonists in stimulating phosphoinositides hydrolysis or arachidonic acid release in these cells. Yet, all these compounds behave as antagonists when compared with carbachol in elevating cAMP levels. In PC12M1 cells, unlike carbachol, the AF series compounds induce only minimal to moderate neurite outgrowth. Yet, these agonists synergize strongly with NGF, which by itself mediates only a mild response. Stimulation of m1AChRs by AF102B, AF150(S) and AF151(S) in PC12M1 cells enhances secretion of beta/A4 amyloid precursor protein derivatives (APPs). The enhanced APPs secretion induced by AF102B is potentiated by NGF. AF102B also stimulates APPs secretion from rat cortical slices. Stimulation of m1AChR in PC12M1 cells with carbachol or AF102B decreases tau phosphorylation as indicated by specific tau-1 mAb and alkaline phosphatase treatment. Due to the above mentioned properties m1 agonists may be of unique value in delaying the progression of **Alzheimer**'s disease (AD). The AF series compounds show a wide safety margin and improve memory and learning deficits in animal models for AD. There is a dearth of clinical reports on m1 agonists. These include studies on AF102B and xanomeline, another m1 selective agonist. We tested AF102B in escalating doses of 20, 40, 60 mg, tid, po, (each dose for 2 weeks) for a total of 10 weeks. This was a single-blind placebo-controlled, parallel-group study in patients with probable AD. AF102B was significantly effective at 40 and 60 mg, tid in the ADAS, ADAS-cognitive and ADAS-word recognition scales. [References: 21]

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☑ 1. Emmerling MR. Spiegel K. Watson MD. Inhibiting the formation of classical C3-convertase on the **Alzheimer**'s beta-**amyloid** peptide. [Journal Article] *Immunopharmacology. 38(1-2):101-9, 1997 Dec.*
UI: 9476121

Abstract • Complete Reference • Get@Pfizer

☑ 2. Carr DB. Goate A. Phil D. Morris JC. Current concepts in the pathogenesis of **Alzheimer**'s disease.[see comment]. [Review] [89 refs] [Journal Article. Review. Review, Tutorial] *American Journal of Medicine. 103(3A):3S-10S, 1997 Sep 22.*
UI: 9344401

Abstract • Complete Reference • Get@Pfizer

☑ 3. Parnetti L. Senin U. Mecocci P. Cognitive enhancement therapy for **Alzheimer**'s disease. The way forward. [Review] [107 refs] [Journal Article. Review. Review, Tutorial] *Drugs. 53(5):752-68, 1997 May.*
UI: 9129864

Abstract • Complete Reference • Get@Pfizer

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Sort Keys			
Primary: - Ascending			
Secondary: - Ascending			

Version: rel9.2.0, SourceID 1.9998.1.313

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Ovid MEDLINE(R) <1966 to March Week 5 2005>

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4	from 3 keep 3, 7, 11, 15, 24, 69...	7
5	from 3 keep 72	1
6	(amyloid aggregation and alzheimer).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	25
7	limit 6 to yr=1997	3
8	secretase inhibitor alzheimer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
9	limit 8 to yr=1997	0
10	from 7 keep 1-3	3
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12	secretase alzheimer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2
13	from 12 keep 2	1

Results of your search: **from 12 [secretase alzheimer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]] keep 2**
Results available: **1**
Result displayed: **1** Logoff

Citation 1.
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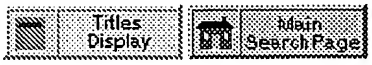
Unique Identifier
1930205
Authors
Maruyama K. Kametani F. Usami M. Yamao-Harigaya W. Tanaka K.
Institution
Department of Molecular Biology, Psychiatric Research Institute of Tokyo, Japan.
Title
"**Secretase**," **Alzheimer** amyloid protein precursor secreting enzyme is not sequence-specific.
Source
Biochemical & Biophysical Research Communications. 179(3):1670-6, 1991 Sep 30.
Abstract
The major pathological change in **Alzheimer**'s disease is the deposition of amyloid beta/A4-

protein (beta P) in the brain. beta P is derived from a small part of the much larger amyloid protein precursor (APP). In the normal condition, APP is cleaved in the interior of beta P, preventing the formation of beta P, by a hypothetical proteinase "**secretase**". To characterize this enzyme, APP and mutated APPs were expressed by cDNA transfection in COS-1 cells, a monkey kidney fibroblast derived cell line. The mutant APPs with the mutations of the proposed cleavage site (Gln686-Lys687) were processed in the same way as wild APP. The deleted mutant APP (deletion of Arg676-Asp694) was also cleaved in a similar way to wild APP. The cleavage site of this deletion mutant was located at the 12 amino acid residues from the predicted membrane spanning domain. Hence, "**secretase**" cleaves APP, depending not on its specific amino acid sequence, but probably on the relative conformation with plasma membrane.



23	exp *ANTI-INFLAMMATORY AGENTS/	141402
24	*ANTI-INFLAMMATORY AGENTS/	18102
25	limit 24 to yr=1997	751
26	Anti-Inflammatory Agents, Non-Steroidal/	30391
27	limit 26 to yr=1997	1882
28	(alzheimer's disease and neuronal anti-inflammatory).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
29	(alzheimer's disease and anti-inflammatory).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	572
30	limit 29 to yr=1997	43
31	from 30 keep 7, 14, 19, 22, 35, 42	6

Results of your search: **from 30 [limit 29 to yr=1997] keep 7, 14, 19, 22, 35, 42**
Results available: **6**
Results displayed: **1-6** Logoff

Citation 1.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9526791

Authors
Verbeek MM. Otte-Holler I. Ruiter DJ. de Waal RM.

Institution
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Title
[Inflammatory mechanisms in the pathogenesis of Alzheimer's **disease**]. [Review] [37 refs] [Dutch]

Source
Tijdschrift voor Gerontologie en Geriatrie. 28(5):213-8, 1997 Oct.

Abstract
Senile plaques belong to the pathological hallmarks of the brains of patients with Alzheimer's **disease**. There is an increasing amount of evidence that the formation of senile plaques is accompanied by an acute phase reaction, involving the production of several inflammation-associated proteins and the activation of microglial cells. The products of these inflammatory reactions may contribute to the fibrillogenesis of the amyloid beta protein, the major constituent of senile plaques. Both fibrils of the amyloid beta protein and products of activated microglial cells may be neurotoxic, leading to neuronal degeneration and to clinical symptoms of dementia. Recent epidemiological findings have drawn attention to the possibility of therapy with **anti-inflammatory** agents. Although the results of these studies suggest a beneficial effect of such therapy, further study is warranted to gain more insight into the fundamental aspects of such treatment as well as to develop specific drugs that have little side-effects. [References: 37]

Citation 2.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9363830
Authors
Scheltens P. van Gool WA.
Institution
Department of Neurology, Academisch Ziekenhuis VU, Amsterdam, The Netherlands. p.scheltens@azvu.nl
Title
Emerging treatments in dementia. [Review] [68 refs]
Source
European Neurology. 38(3):184-9, 1997.
Abstract
Dementia is one of the most common organic mental syndromes, usually caused by Alzheimer's **disease** (AD) or vascular dementia (VD) or both. Regarding AD we review the state or the art of the cholinergic approach and discuss some future options regarding preventive and nonsymptomatic strategies. Therapy for VD will consist mainly in influencing and preventing cerebrovascular pathology, because operational criteria for the diagnosis have only recently been proposed and are being discussed widely. One of the crucial problems here lies in the distinction between VD and AD and the recognition that the two disorders may be coexistent more often than assumed; the role of white matter changes seems to be particularly important. The same goes for the recognition that AD ist not a single entity. The question of heterogeneity may be solved when different therapeutic strategies are found for different subtypes. The focus of future plans should be on preventive strategies combined with an early diagnosis. [References: 68]

Citation 3.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9334509
Authors
Cummings JL. Mendez MF.
Institution
Department of Neurology, UCLA School of Medicine, USA.
Title
Alzheimer's **disease**: cognitive and behavioral pharmacotherapy. [Review] [57 refs]
Source
Connecticut Medicine. 61(9):543-52, 1997 Sep.
Abstract
Alzheimer's **disease** is a progressive degenerative **disease** with cognitive and behavioral manifestations. The pathophysiology of Alzheimer's **disease** is increasingly well understood, leading to approved and experimental therapies. Mutations on chromosomes 1, 14, and 21 can cause the **disease** and are sometimes present in patients with early onset Alzheimer's **disease**. Older patients--comprising the majority of Alzheimer's **disease** victims--have a variety of risk factors including age, gender, history of head trauma, low education level, and apolipoprotein genotype. The pathogenetic process leads to regional cell loss and biochemical deficits. The mutations and risk factors lead to increased amyloid production or accumulation and nerve cell death. Neurons atrophy in the cerebral cortex and in source nuclei of important neurotransmitters. The deficiency of acetylcholine can be partially remedied by cholinesterase inhibitors that produce modest cognitive and behavioral improvement. Anti-amyloid agents, antioxidants, **anti-inflammatory** drugs, estrogens, and calcium channel blockers may all slow the progression of Alzheimer's **disease** by interfering with specific steps within the **disease**

cascade. Neuropsychiatric symptoms are also common in Alzheimer's **disease** and may be ameliorated by conventional psychotropic agents. Clinicians can currently offer substantial help to Alzheimer's **disease** patients, and the future promises more effective pharmacotherapy. [References: 57]

Citation 4.
Link to... Complete Reference • Get@Pfizer

Unique Identifier
9218980
Authors
Senin U. Cherubini A. Palumbo B. Mecocci P.
Institution
Department of Gerontology and Geriatrics, University of Perugia, Italy.
Title
Pharmaceutical treatment of cognitive disorders in Alzheimer's **disease**.
Source
Functional Neurology. 12(3-4):211-2, 1997 May-Aug.

Citation 5.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9129864
Authors
Parnetti L. Senin U. Mecocci P.
Institution
Perugia University, Italy. parnetti@unipg.it
Title
Cognitive enhancement therapy for Alzheimer's **disease**. The way forward. [Review] [107 refs]
Source
Drugs. 53(5):752-68, 1997 May.
Abstract
Although at present there is no definitive treatment or cure for Alzheimer's **disease**, different pharmacological strategies are being actively investigated. At present, cholinergic therapy and nootropics and some neuronotrophic agents represent the available approaches to symptomatic treatment of Alzheimer's **disease**. The use of cholinesterase inhibitors (ChEI) constitutes the best cholinergic approach to increase acetylcholine levels. Available data suggest that about 15 to 40% of Alzheimer's **disease** patients show a varying degree of cognitive improvement while taking these medications; however, haematological complications (neutropenia or agranulocytosis), together with hepatotoxicity, need to be considered carefully. Recent data suggest that long term administration of nootropics may lead to a significant improvement of cognitive functions in Alzheimer's **disease** patients compared with untreated individuals, having excellent tolerability. Protocols for the intracerebroventricular administration of neuronotrophic substances are also ongoing. The most promising approaches for the future currently undergoing investigation involve attempts to slow the production of beta-amyloid and/or to inhibit beta-amyloid aggregation. Another rational therapeutic approach would be to inhibit the formation of paired helical filaments (PHF) by increasing and/or modulating the activities of protein phosphatases and kinases. Antioxidant therapy should disrupt or prevent the free radical/beta-amyloid recirculating cascade and the progressive neurodegeneration. Idebenone, a synthetic

compound acting as an 'electron trapper' and free radical scavenger, has shown some efficacy in degenerative and vascular dementia; at present, other different molecules having antioxidative properties [lazaroids (21-aminosteroids), pyrrolopyrimidines, nitric oxide blockers, selegiline, some vitamins] are under investigation. Lowering absorption or brain tissue concentrations of aluminium also offers possible therapeutic opportunities for slowing the rate of clinical progression of the **disease**; in this sense, some evidence exists using the aluminium chelating agent deferoxamine (desferrioxamine). Inflammation also may play a significant pathogenetic role in Alzheimer's **disease**. As shown by several retrospective analyses, there is an inverse association of **anti-inflammatory** drug use with the frequency of Alzheimer's **disease** diagnosis. Consequently, clinical trials using both nonsteroidal and steroidal molecules have been proposed. These lines of pharmacological intervention represent an important premise for future therapeutic strategies capable of counteracting the pathogenesis of Alzheimer's **disease**. [References: 107]

Citation 6.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
8996836
Authors
Aisen PS.
Institution
Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029, USA.
Title
Inflammation and Alzheimer's **disease**: mechanisms and therapeutic strategies. [Review] [63 refs]
Source
Gerontology. 43(1-2):143-9, 1997.
Abstract
Inflammatory mechanisms in the brain may contribute to the neurodegenerative process in Alzheimer's **disease**. The cerebral acute-phase response mediated by inflammatory cytokines, the complement cascade, and the accumulation of activated microglial cells are appropriate targets for **anti-inflammatory** intervention. Pilot studies showed that tolerable doses of prednisone suppress the peripheral acute-phase response in Alzheimer's **disease**, and a multicenter therapeutic trial of prednisone is in progress. Two other **anti-inflammatory** drugs, hydroxychloroquine and colchicine, are also under investigation. [References: 63]

Titles Display | Main Search Page

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24	*ANTI-INFLAMMATORY AGENTS/	18102
25	limit 24 to yr=1997	751
26	Anti-Inflammatory Agents, Non-Steroidal/	30391
27	limit 26 to yr=1997	1882
28	(alzheimer's disease and neuronal anti-inflammatory).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	0
29	(alzheimer's disease and anti-inflammatory).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	572
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Results available: **9**
Results displayed: **1-9** Logoff

Citation 1.
Link to... Complete Reference • Get@Pfizer

Unique Identifier
9459928
Authors
Cornell S.
Title
Another use for **estrogen**? Hormone may influence Alzheimer's **disease**.[see comment].
Comments
Comment in: Adv Nurse Pract. 1997 Jun;5(6):8; PMID: 9459921
Source
Advance for Nurse Practitioners. 5(6):49-50, 53, 1997 Jun.

Citation 2.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9406879
Authors
Mook-Jung I. Joo I. Sohn S. Kwon HJ. Huh K. Jung MW.
Institution
Department of Neurology, School of Medicine, Institute for Medical Sciences, Ajou University, Suwon, South Korea. inhee@skull.ajou.ac.kr
Title

Estrogen blocks neurotoxic effects of beta-amyloid (1-42) and induces neurite extension on B103 cells.

Source

Neuroscience Letters. 235(3):101-4, 1997 Oct 17.

Abstract

Clinical studies have shown that **estrogen** replacement therapy is associated with reduced risk of Alzheimer's **disease** (AD). We tested whether or not **estrogen** blocks neurotoxic effects of beta-amyloid (1-42) (A beta1-42) on cultured B103 cells. A beta1-42 (1 microM) induced typical necrotic cell death, as revealed by light and electron microscopic examinations. Co-administration of **estrogen** not only blocked A beta1-42 toxicity to a large degree, but also enhanced neurite extension. Pretreatment with **estrogen** was even more effective in blocking A beta1-42 toxicity. When added 18 h after the beginning of A beta1-42 treatment, **estrogen** was still effective in halting the progress of cell death and enhancing neurite extension. The protection against A beta1-42-induced neuronal death by **estrogen** was unlikely due to a blockade of lipid peroxidation injury, since **estrogen** completely failed to attenuate ferrous chloride-induced cell death. These results demonstrate that **estrogen** blocks A beta1-42-induced neurotoxicity and enhances neurite extension on B103 cells, both of which may well be underlying mechanisms of beneficial effects of **estrogen** in AD.

Citation 3.

Link to... Abstract • Complete Reference • Article Review • Get@Pfizer

Unique Identifier

9393381

Authors

Haskell SG. Richardson ED. Horwitz RI.

Institution

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA.

Title

The effect of **estrogen** replacement therapy on cognitive function in women: a critical review of the literature. [Review] [58 refs]

Source

Journal of Clinical Epidemiology. 50(11):1249-64, 1997 Nov.

Abstract

OBJECTIVE: To conduct a review of the available clinical trials to determine whether sufficient evidence exists to support the conclusion that **estrogen** replacement therapy has a beneficial effect on cognitive performance in post-menopausal women and in women with Alzheimer's **disease**. Studies were identified through a MEDLINE search of all English-language publications between 1970 and 1996 in which the words **estrogen** and cognition or **estrogen** and memory appeared. **DATA EXTRACTION:** Data were extracted for each study, including features of subjects and eligibility criteria, duration of follow-up, and treatment regimen. Baseline characteristics were evaluated, including age; menopausal status; follicle-stimulating hormone, luteinizing hormone, and estradiol levels; mood; and measures of cognitive function. Psychological tests were evaluated for construct validity. **RESULTS:** Nineteen studies were reviewed, including 10 randomized trials of **estrogen** replacement therapy versus placebo. Extreme heterogeneity among subjects and variability in the use of cognitive measures across the studies precluded performing a quantitative summary. Of the 10 randomized trials, eight claimed therapeutic benefits for **estrogen** therapy, three of which reported significant improvements in memory and two of which showed improvements in attention. These studies did not control for potential confounds such as depression and vasomotor symptoms. Of the nine observational

studies, five found a significant association between **estrogen** use and cognitive function. **CONCLUSION:** Although several observational studies provide encouraging evidence for the beneficial effect of **estrogen** on cognitive function, there is currently inadequate evidence available from randomized, controlled trials to support the conclusion that **estrogen** replacement therapy improves cognitive function in post-menopausal women or women with Alzheimer's dementia. [References: 58]

Citation 4.

Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier

9360809

Authors

Beckmann CR.

Institution

Department of Obstetrics and Gynecology, University of Missouri at Kansas City, School of Medicine, Truman Medical Center West 64108, USA.

Title

Alzheimer's **disease**: an **estrogen** link?. [Review] [76 refs]

Source

Current Opinion in Obstetrics & Gynecology. 9(5):295-9, 1997 Oct.

Abstract

The prospect that Alzheimer's **disease** is caused by or related to **estrogen** deficiency, and treatable or even preventable by **estrogen** replacement therapy, is alluring. At present, evidence that Alzheimer's **disease** is an **estrogen** deficiency **disease** is lacking. However, there is much evidence that beneficial effects of **estrogen** replacement therapy on the areas of the brain associated with Alzheimer's **disease** may prevent or slow the progress of Alzheimer's **disease** or the expression of Alzheimer's **disease** symptoms. Given the proven value of **estrogen** replacement therapy for most women for other indications, this probable additional benefit is welcome. Further research is needed. [References: 76]

Citation 5.

Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier

9344406

Authors

Schneider LS. Farlow MR. Pogoda JM.

Institution

Department of Psychiatry and the Behavioral Sciences, School of Medicine, University of Southern California, Los Angeles 90033, USA.

Title

Potential role for **estrogen** replacement in the treatment of Alzheimer's dementia.

Source

American Journal of Medicine. 103(3A):46S-50S, 1997 Sep 22.

Abstract

In light of evidence that **estrogen** replacement therapy (ERT) might affect cholinergic function, we examined possible effects of ERT on clinical and cognitive responses to the cholinesterase inhibitor tacrine in women with Alzheimer's **disease** (AD). In a previously reported 30-week, randomized, double-blind, placebo-controlled, multicenter clinical trial, 14.5% of 318 women

with evaluable data had been receiving ERT prior to randomization. Patients were randomly assigned to receive placebo or one of three ascending dosages of tacrine (maximum dosages of 80 mg/day, 120 mg/day, or 160 mg/day). Women completing the trial receiving ERT and tacrine improved more than women not receiving ERT who were randomized to tacrine or to placebo as assessed by cognitive ($p < 0.01$), clinical ($p = 0.02$), caregiver ($p = 0.006$), and mental status ($p = 0.07$) ratings. Using an intent-to-treat analysis, they improved significantly on cognitive ratings ($p = 0.01$). These results provide evidence that prior and continuing ERT may enhance response to tacrine in women with AD. Randomized trials are needed.

Citation 6.
Link to... Complete Reference • Get@Pfizer

Unique Identifier
9344405
Authors
Birge SJ. Mortel KF.
Institution
Older Adult Health Center, Washington University School of Medicine, St. Louis, Missouri 63108-2293, USA.
Title
Estrogen and the treatment of Alzheimer's **disease**. [Review] [97 refs]
Source
American Journal of Medicine. 103(3A):36S-45S, 1997 Sep 22.

Citation 7.
Link to... Abstract • Complete Reference • Get@Pfizer

Unique Identifier
9329702
Authors
Schneider LS. Farlow M.
Institution
Department of Psychiatry, School of Medicine, Los Angeles, California, USA. lschneid@hsc.usc.edu
Title
Combined tacrine and **estrogen** replacement therapy in patients with Alzheimer's **disease**.
Source
Annals of the New York Academy of Sciences. 826:317-22, 1997 Sep 26.
Abstract
In light of evidence that **estrogen** replacement might affect cholinergic function, we examined possible effects of **estrogen** replacement therapy (ERT) on clinical response to the cholinesterase inhibitor tacrine in women with Alzheimer's **disease** (AD). In a previously reported 30-week, randomized, double-blind, placebo-controlled, multicenter clinical trial, 14.5% of 318 women with evaluable data had been receiving ERT before randomization. They were randomly assigned to receive placebo or tacrine. Women receiving ERT who were randomized to tacrine improved more than women not receiving ERT who were randomized either to tacrine or to placebo as assessed by cognitive ($p < 0.01$) and clinical global ($p = 0.02$) tests. These results provide evidence that prior and continuing ERT may enhance response to tacrine in women with AD. Furthermore, among women on ERT receiving tacrine, there tended to be greater improvement relative to placebo among those without an APOE-epsilon 4 allele. Randomized

trials are needed.

Citation 8.

Link to... Abstract • Complete Reference • Ovid Full Text • Get@Pfizer

Unique Identifier

9191758

Authors

Kawas C. Resnick S. Morrison A. Brookmeyer R. Corrada M. Zonderman A. Bacal C. Lingle DD. Metter E.

Institution

Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Title

A prospective study of **estrogen** replacement therapy and the risk of developing Alzheimer's **disease**: the Baltimore Longitudinal Study of Aging.[erratum appears in Neurology 1998 Aug;51 (2):654].

Source

Neurology. 48(6):1517-21, 1997 Jun.

Abstract

Previous reports have suggested that **estrogen** replacement therapy (ERT) in women may exert a protective effect on their risk of developing Alzheimer's **disease** (AD). We investigated this relationship in the Baltimore Longitudinal Study of Aging (BLSA), a prospective multidisciplinary study of normal aging conducted by the National Institute on Aging. The sample consisted of 472 post- or perimenopausal women followed for up to 16 years in the BLSA. We documented ERT prospectively at each BLSA visit, and we categorized women who had used oral or transdermal **estrogens** at anytime as ERT users. We used Cox proportional hazards models with time-dependent covariates to estimate the relative risk of developing AD after ERT as compared with women who had not used **estrogen** replacement. Approximately 45% of the women in the cohort had used ERT, and we diagnosed 34 incident cases of AD (NINCDS/ADRDA criteria) during follow-up, including nine **estrogen** users. After adjusting for education, the relative risk for AD in ERT users as compared with nonusers was 0.46 (95% CI, 0.209-0.997), indicating a reduced risk of AD for women who had reported the use of **estrogen**. Our data did not show an effect for duration of ERT usage. Our finding offers additional support for a protective influence of **estrogen** in AD. Randomized clinical trials are necessary to confirm this association, which could have significant public health impact.

Citation 9.

Link to... Abstract • Complete Reference • Ovid Full Text • Topic Review • Get@Pfizer

Unique Identifier

9153165

Authors

Birge SJ.

Institution

Division of Geriatrics, Washington School of Medicine, St. Louis, MO 63108, USA.

Title

The role of **estrogen** in the treatment of Alzheimer's **disease**. [Review] [55 refs]

Source

Neurology. 48(5 Suppl 7):S36-41, 1997 May.

Abstract

Multiple factors appear to contribute to the expression of Alzheimer's **disease** (AD). About 30 percent of cases of dementia of the Alzheimer's type can be attributed to genetic factors. These observations raise the possibility of identifying multiple interventions that may modify the **disease** process and, therefore, the clinical expression of the dementia. Prominent among factors that may contribute to dementia and, specifically, to dementia of the Alzheimer's type is cerebral vascular **disease**. **Estrogen** is a potent factor that not only prevents vascular **disease** but also improves blood flow in **diseased** vessels, including blood flow in regions on the brain affected by AD. **Estrogen** also has direct effects on neuronal function that may play an important role not only in the preservation of neurons but in repair of neurons damaged by **disease** process. These effects of **estrogen** on the CNS suggest that the hormone may be effective not only in the prevention of dementia but also in its treatment. The results of clinical trials, reviewed in this presentation, are very promising but are limited by the paucity of subjects and often the lack of adequate controls. Larger, randomized, placebo-controlled trials are needed to definitively establish the efficacy of **estrogen** in the treatment of dementia of the Alzheimer's type. [References: 55]